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10/559,819	06/02/2006	Pierre Jurdic	0070663-000003	9643

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EXAMINER	
NGUYEN, QUANG	
ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
02/13/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ADIPFDD@bipc.com

Office Action Summary	Application No.	Applicant(s)	
	10/559,819	JURDIC ET AL.	
	Examiner	Art Unit	
	QUANG NGUYEN, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14 and 16-21* is/are pending in the application.

4a) Of the above claim(s) *7-14,16,18,19 and 21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,17 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 June 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/28/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-14 and 16-21 are pending in the present application.

Applicant's election of Group I in the reply filed on 7/3/08 and the species of rheumatoid arthritis being induced in the bone system model in the reply on 11/24/09 are acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Accordingly, claims 7-14, 16, 18-19 and 21 are withdrawn from further consideration because they are directed to non-elected inventions and non-elected species.

Therefore, claims 1-6, 17 and 20 are examined herein with the aforementioned elected species.

Specification

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. **The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided**. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The abstract is objected because it contains the term "said" on line 5 of the abstract.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-4 are rejected under 35 USC 101 because the claimed invention is directed to non-statutory subject matter.

The claims are directed to a bone system model comprising a mineralized matrix, a layer of osteoblasts at confluence and/or osteoblast nodules on said matrix, and osteoclasts on said layer and/or said noducles. It is also noted that that the osteclasts are not necessarily in direct contact with the osteoblasts. As written, the claims do not sufficiently distinguish over **a remodeling bone system occurring naturally in a mammal** because the claims do not particularly point out any non-naturally occurring differences between the claimed product and the naturally occurring product. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject mater. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 recites the limitation "the human bone system" in line 2 of the claim. There is insufficient antecedent basis for this limitation in the claim. Which specific human bone system do Applicant refer to? Clarification is requested because the metes and bounds of the claim are not clearly determined. For the purpose of a compact prosecution, the Examiner interprets the claim to refer to mimic any human bone system.

Claim 20 is vague and indefinite in that the metes and bounds of the term “derived from” are unclear. It is unclear the nature and number of steps required to obtain a “derivative” of osteoblasts and/or osteoclasts. The term implies a number of different steps that may or may not result in a change in the functional characteristics of osteoblasts and/or osteoclasts from the source that it is “derived from”. It would be remedial to amend the claim language to use the term “obtained from”, which implies a more direct method of acquiring osteoblasts and/or osteoclasts. Additionally, the term “normal animals” is a subjective term because to some certain animals are normal while to others the same animals are not normal. Furthermore, it is unclear what is the nexus between the phrase “the osteoblasts and/or the osteoclasts are derived from normal animals, and wherein rheumatoid arthritis has been induced in said chemically in situ “ and the phrases “and/or results from knock-out animals are transgenic for any molecule

capable of inducing rheumatoid arthritis" and "or from animals having been given injections of collagen type II, or of any other substances capable of inducing an articular inflammation mimicking rheumatoid arthritis". How do osteoblasts and/osteoclasts derived from normal animals have anything to do with results from knock-out animals or animals given injections of collagen type II or any other substances as claimed? Clarification is requested because the metes and bounds of the claim are not clearly determined as written.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Van Blitterswijk et al. (US 6,152,964).

Van Blitterswijk et al already disclosed an assay to examine the influence of osteoblast derived factors on osteoclastic resorption by culturing young rat osteoblasts on calcium phosphate samples (mineralized matrix), followed by the culture of young rat osteoclasts (see at least example 3 in cols 5-6). Van Blitterswijk et al also disclosed that osteoclasts were present on the materials and resorption of the mineralized matrix formed by the osteoblasts was seen, and concluded that osteoclasts are capable of resorbing certain calcium phosphates but only when osteoblasts are firstly cultured on

the substrates suggesting that factors produced by osteoblasts have a stimulating effect on osteoclastic activity. It is further noted that disclosed assay system taught by Van Blitterswijk et al mimics a human bone resorption system.

The teachings of Van Blitterswijk et al. meet all the limitation of the instant claims as written. Therefore, the reference anticipates the instant claims.

Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Kikuchi et al. (Biomaterials 22:1705-1711, 2001; IDS).

Kikuchi et al already disclosed a bone-like hydroxyapatite (a derivative of calcium phosphate)/collagen nanocomposite being implanted into a 20 mm bone defect in a tibiae of a Beagle for up to 12 weeks, and under such conditions the nanocomposite implant was resorbed by osteoclasts on top of a layer of elongated osteoblast cells deposited new bone as shown in Figure 6 (see at least the abstract; page 1706, col. 2, last paragraph continues to top of first paragraph of col. 1 on page 1707; page 1709, col. 1, last paragraph).

Since the claims do not require that the osteoclasts are in direct contact and on top of osteoblasts, the teachings of Kikuchi et al meet all the limitation of the instant claims as broadly written. Therefore, the reference anticipates the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shibutani et al (J. Biomed. Mater Res. 50:153-159, 2000; IDS) in view of Chambers et al. (J. Cell Sci 76:155-165, 1985) and Rovira et al (Biomatrials 17:1535-1540, 1995; IDS).

Shibutani et al already disclosed **a system comprising seeding osteoclasts on glass slides coated with apatite-collagen complexes (ACC) for measurement of osteoclastic resportion activity**, and found that osteoclasts could resorb the apatite particles and coated collagen on the glass slide (see at least the abstract and Materials and Methods section). Shibutani et al also teach that the ACC-coated glass slide could be useful for investigating both the function and metabolic activities of osteoclasts (page 159, col. 1, first paragraph).

Shibutani et al do not teach specifically a system comprising seeding osteoclasts on a layer of confluent osteoblasts and/or osteoblast nodules on a mineralized matrix for measurement of osteoclastic resorption activity.

At the effective filing date of the present application, Chamber et al already taught that **unmineralized osteoid is present on all bone surfaces, and that osteoclasts do not resorb bone from native bone surfaces** (see at least the Introduction section). Chamber et al also demonstrated **that calvarial cells (osteoblasts) are capable of osteoid destruction, and one mechanism by which osteoblasts induce osteoclastic bone resorption maybe though digestion of unmineralized organic material that covers bone surfaces, to expose the underlying resoroption-stimulating bone mineral for osteoclastic contact (**see at least the abstract). Chamber et al further noted that **it is of interest that in a model of bone resorption in which osteoclasts can be induced to resorb bone simultaneously in a well-defined temporospatial sequence *in vivo***, the earliest observation, before multinucleate cells appear, is obliteration of unmineralized osteoid from the bone surface; and that **a final common pathway for osteoblastic stimulation of osteoclastic bone resorption in response to local and systemic systems may be through proteolytic digestion of surface osteoid to expose bone mineral to osteoclastic contact** (see page 164, last two paragraphs).

Additionally, at the effective filing date of the present application Rovira et al also taught that **human osteoblasts are capable of attaching to and colonizing a calcium phosphate/elastin-solubilized peptide-collagen composite without loss of**

their phenotypic expression after 1 month in culture (see at least the abstract and page 1535, col. 2, second full paragraph).

It would have been obvious for an ordinary skilled artisan to modify the osteoclastic resorption system of Shibutani et al by further coating the ACC-glass slides with a confluent layer of osteoblasts and/or osteoblast nodules prior to seeding the osteoclasts to model or mimic a bone resorption system on native bone surfaces to study metabolic activities of osteoclasts in light of the teachings of Chamber et al and Rovira et al as presented above.

An ordinary skilled artisan would have been motivated to carry out the above modification because Chambers et al already taught that unmineralized osteoid is present on all bone surfaces, osteoclasts do not resorb bone from native bone surfaces and that one mechanism by which osteoblasts induce osteoclastic bone resorption is though digestion of unmineralized organic material that covers bone surfaces, to expose the underlying resoroption-stimulating bone mineral for osteoclastic contact. Moreover, Rovira et al also demonstrated that human osteoblasts are capable of attaching to and colonizing a calcium phosphate/elastin-solubilized peptide-collagen composite without loss of their phenotypic expression after 1 month in culture.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Shibutani et al., Chambers et al and Rovira et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Shibutani et al (J. Biomed. Mater Res. 50:153-159, 2000; IDS) in view of Chambers et al. (J. Cell Sci 76:155-165, 1985) and Rovira et al (Biomatrials 17:1535-1540, 1995; IDS) as applied to claims 1-4 above, and further in view of Traianedes et al. (Endocrinology 139:3178-3184; IDS).

The combined teachings of Shibutani et al, Chambers et al and Rovira et al were already presented above. However, none of references teaches further inducing rheumatoid arthritis in the modified bone system by chemically *in situ*.

At the effective filing date of the present application, Traianedes et al already taught that **application of exogenous leukotriene *in vitro* and *in vivo* results in increased osteoclast formation and resorption, and that 5-lipooxygenase (5-LO) metabolites also inhibit bone and/or bone nodule formation on cell cultures** (see at least the abstract). Traianedes et al further disclosed that **5-LO metabolites may be responsible for decreased osteoblast function or decreased bone formation in conditions of elevated 5-LO metabolite production such as the acute phase inflammatory response and rheumatoid arthritis** (page 3182, col. 2, last two lines continue to first paragraph of col. 1 on page 3183).

It would have been obvious for an ordinary skilled artisan to further modify the combined teachings of Shibutani et al, Chamber et al and Rovira et al by introducing exogenous leukotriene or 5-LO metabolites into the modified model of bone resorption

to mimic the conditions found in rheumatoid arthritis to study metabolic activities of osteoclasts.

An ordinary skilled artisan would have been motivated to carry out the above modification because Traianedes et al already disclosed that production of 5-LO metabolites are elevated in rheumatoid arthritis.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Shibutani et al., Chambers et al, Rovira et al and Traianedes et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Shibutani et al (J. Biomed. Mater Res. 50:153-159, 2000; IDS) in view of Chambers et al. (J. Cell Sci 76:155-165, 1985) and Rovira et al (Biomatrials 17:1535-1540, 1995; IDS) as applied to claims 1-4 above, and further in view of Rodan et al. (US 6,093,533).

The combined teachings of Shibutani et al, Chambers et al and Rovira et al were already presented above. However, none of references teaches the use of the system for testing or assaying a substance.

At the effective filing date of the present application, Rodan et al already taught the use of an assay comprising an osteoclast-enriched population of cells containing osteoblasts on a bone slice to test inhibitory or stimulatory effect of a test substance, including a drug that inhibits bone resorption (see at least col. 5, lines 38-56).

It would have been obvious for an ordinary skilled artisan to further modify the combined teachings of Shibutani et al, Chamber et al and Rovira et al by also using the modified osteoclastic resorption system to test inhibitory or stimulatory effect of a test substance as well as for a drug that inhibits bone resorption.

An ordinary skilled artisan would have been motivated to carry out the above modification because Rodan et al already taught successfully using an assay comprising an osteoclast-enriched population of cells containing osteoblasts on a bone slice to test inhibitory or stimulatory effect of a test substance.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Shibutani et al., Chambers et al, Rovira et al and Rodan et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Shibutani et al (J. Biomed. Mater Res. 50:153-159, 2000; IDS) in view of Chambers et al. (J. Cell Sci 76:155-165, 1985) and Rovira et al (Biomatrials 17:1535-1540, 1995; IDS) as applied to claims 1-4 above, and further in view of Choi et al. (US 2004/0092714).

The combined teachings of Shibutani et al, Chambers et al and Rovira et al were already presented above. However, none of references teaches the use of genetically modified osteclasts.

At the effective filing date of the present application, Choi et al already taught a method for modulating osteoclast activities comprising contacting an osteoclast cell with a compound that modulates activity of an OSCAR (osteoclast associated receptor) that includes an antisense, ribozyme and triple-helix forming nucleic acid (see at least paragraph 14).

It would have been obvious for an ordinary skilled artisan to further modify the combined teachings of Shibutani et al, Chamber et al and Rovira et al by also studying metabolic activities of osteoclasts transformed or transfected with compounds such as antisense, ribozyme and triple-helix forming nucleic acid specific against OSCAR gene (such cells would fall within the broad scope of osteoclasts being genetically modified) on the modified system that mimicks native bone surface in light of the teachings of Choi et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because Choi et al already taught that compounds such as antisense, ribozyme and triple-helix forming nucleic acid specific against OSCAR gene could modulate osteoclast cell activities.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Shibutani et al., Chambers et al, Rovira et al and Choi et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Shibutani et al (J. Biomed. Mater Res. 50:153-159, 2000; IDS) in view of Chambers et al. (J. Cell Sci 76:155-165, 1985) and Rovira et al (Biomatrials 17:1535-1540, 1995; IDS) as applied to claims 1-4 above, and further in view of Sun et al. (Biomed. Mater Res. 45:311-321, 1999; IDS).

The combined teachings of Shibutani et al, Chambers et al and Rovira et al were already presented above. However, none of references teaches the use of osteoclasts to osteoblasts in the ratio of approximately 1/10 to 1/25.

At the effective filing date of the present application, Sun et al already studied the influence of hydroxyapatite particles on osteoclast cell activities in an *in vitro* osteoblast/osteoclast co-cultured model in which the ratio of osteoclasts/osteoblasts in initial cultures start from about 8.6%, within the range of 1/10 to 1/25 ratio as claimed (see at least the abstract; Table II and page 314, col. 1, last two lines continue to the paragraph of col. 2).

Accordingly, it would have been obvious for an ordinary skilled artisan to further modify the combined teachings of Shibutani et al, Chamber et al and Rovira et al by also using the ratio of osteoclasts/osteoblasts from approximately 1/10 to 1/25 in the modified bone resorption system.

An ordinary skilled artisan would have been motivated to carry out the above modification because Sun et al already used successfully an osteoblast/osteoclast co-cultured model in which the ratio of osteoclasts/osteoblasts in initial cultures starts from about 8.6% to test the influence of hydroxyapatite particles on osteoclast cell activities.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Shibutani et al., Chambers et al, Rovira et al and Sun et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/QUANG NGUYEN/
Primary Examiner, Art Unit 1633